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UCRL-CONF-212194

Evolutionary Theories of Detection

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May 12, 2005

DHS IEEE Conference
Boston, MA, United States
April 25, 2005 through April 28, 2005

EVOLUTIONARY THEORIES OF DETECTION

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ABSTRACT

Current, mid-term and long range technologies for detection of pathogens and toxins are briefly described in the context of performance metrics and operational scenarios. Predictive (evolutionary) and speculative (revolutionary) assessments are given with trade-offs identified, where possible, among competing performance goals.

Detection Basics

Detection theory is an integral part of statistical communication theory and is a relatively mature discipline. These theories and engineering approaches enabled radio communication, RADAR, and numerous other applications including coding, computations and imaging. Basically, detection is a decision that is based on statistical analysis.

A binary decision is the statistical analysis that concludes Hypothesis 1 (H1) is true. Otherwise, Hypothesis 0 (H0), known as the null hypothesis, is assumed. A "positive" is selection of Hypothesis 1. The conditional probabilities for a true positive (select H1, when H1 is true) and a false positive (select H1, when H1 is not true), are often used to describe detection performance. In many applications, the data can be reduced to a single scalar that we will call **s**. The detection decision is made by comparing **s** to a threshold that we designate as T. In summary,

Probability of true positive = P(say H1 | H1 is true) = P(**s** > T | H1)

Probability of false positive = P(say H1 | H1 is false) = P(**s** > T | H0)

In the simple case where H1 and H0 are statistically distinct, selection of a threshold T is straightforward and intuitive (see Fig. 1). As is shown in Fig. 2, once the distributions for the two hypotheses overlap, selection of the threshold T becomes a trade-off between sensitivity (the probability of detecting a true positive) and the probability of a false positive. This trade-off is

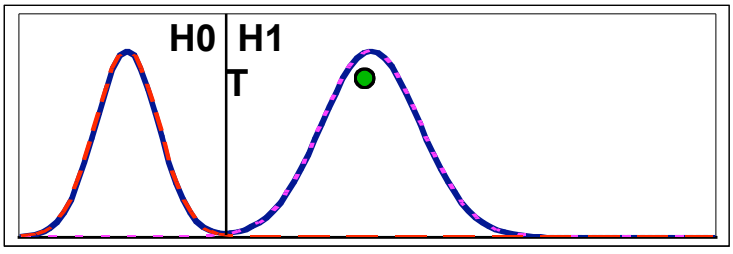

Fig. 1 Selection of a threshold is intuitive for statistically separate hypotheses

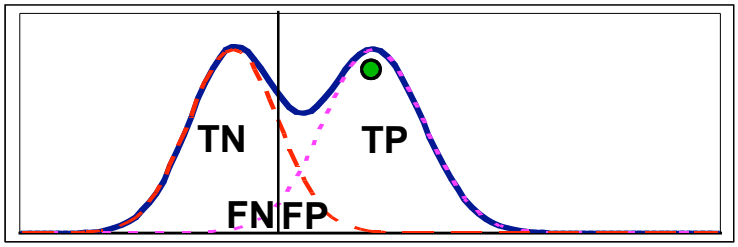

Fig. 2 For overlapping hypotheses, the threshold determines true positive (TP), false positive (FP), true negative (TN), and false negative (FN) probabilities.

fundamental to detection systems. Receiver Operator Characteristic (ROC) curves are used to compare the relationship between these probabilities for different thresholds. As shown in Fig. 3, an ideal detection system would operate in the upper left corner of the ROC curve—probability of detection is one and zero false positives. In some applications, the signal or the noise in the system has a statistical structure to it. This allows multiple samples to help determine which of the two hypotheses is true with far greater accuracy than a single measurement could.

What does this mathematics mean for operational biodetection systems? A true positive is detecting the presence of a pathogen. A false positive is detecting a pathogen as present when there is none. For pristine samples, like spiked pathogen in saline, a high performing detection threshold T can be readily established. This is similar to the example in Fig. 1. This is still a useful experiment to estimate the limit of detection for an instrument but it may not predict performance for complex samples. The "noise" faced by a biodetection system includes environmental backgrounds, inhibitors and interferents that change performance as well as imperfect specificity of the instruments and signatures.

Operational detection systems must consider the impact to conduct of operations (CONOPs). The CONOPS can be equal or greater in importance than technical performance. Different sensitivity and error rates for different thresholds will impact the CONOPs. For instance, the

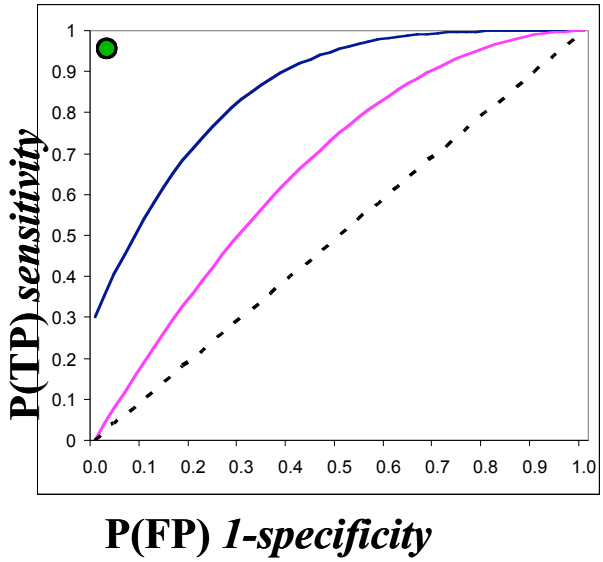

Fig. 3 Representative Receiver Operator Characteristic (ROC) curves for changing detection threshold. The upper left dot is an idealized detector.

public health reaction would be considerably different for high confidence detection of pathogen than for very low confidence. However, a false positive may invoke unneeded response resources and lower confidence in the system. As discussed, increasing the probability of detection will increase the probability of false positives. Communication among instrument developers, end-users and policy makers are essential to establish appropriate understanding of how to take data from biodetection systems and provide actionable information.

Metrics for Biodetection Systems

For simplicity, this discussion is restricted to instrumentation for the detection of aerosolized pathogens. The approach is appropriate for other instruments for water, clinical, agricultural, and facilities as well as for epidemiological detection and warning.

For pathogens that cause diseases with known treatments, early detection allows early intervention, and increases significantly the probability of successful outcome. For pathogens with no known treatment, early detection allows information dissemination and quarantine to be used early and appropriately, making them more effective. Quarantine is obviously best utilized before geographic spread of a disease. Information dissemination, for instance how the disease is transmitted, can greatly impact spread of the disease. For both existing treatment and no known treatment, the key parameter that biodetection systems address is time.

The metrics being used to evaluate and design detection systems are driven by the goal of reducing time. Some representative metrics are geographic coverage—number of collectors, locations, and volume of air collected per unit time; temporal coverage—sampling time and processing time; sensitivity and false alarm rate; and efficiency at all stages.

It is difficult to have a single invariant measure for detector performance. The closest measure that we have is ACBLA-minutes: *Aerosol Containing Bioagent per Liter of Air – Minute*. This allows comparison, albeit not perfectly, of different systems independent of how long they collect, flow rates, etc. In addition, the fundamental units for "bioagent" vary with colony forming units (CFU) used for bacteria and spores, plaque forming units (PFU) for viruses, and nanograms (ng) for toxins.

Special Event Biodetection Example

The BASIS system designed by Lawrence Livermore and Los Alamos National Laboratories for use at a special event—the Salt Lake City Winter Olympics in 2002. The term "design" is misleading because, although LLNL and LANL did design the technical system, the overall requirements were developed in a highly interactive environment with inputs from event organizers, public health, and law enforcement. As with setting detection thresholds in complex environments, compromises among competing information needs were developed. A few of the requirements from the 2002 BASIS system will be reviewed here.

First and foremost, there was a requirement that there be zero false positives. For an event like the Olympics where athletes train for years, there could be no canceling or delaying of venues without the scientific basis to justify such extreme measures. This does not mean that the BASIS system cannot or will never false positive. It does mean that the probability that the system would produce a false alarm during the Olympics was very small. In addition to the rigorous

testing of the hardware, the signatures, the reagents, and the protocols were also tested and exercised before the Olympics. We also deployed a small version of BASIS to Salt Lake City a year before the Olympics in the winter 2001. This allowed us to challenge the system with arguably the most representative background for the Olympics in 2002.

Public health experts provided desired timelines for sample collection and processing based on estimating health effects from representative pathogen concentrations in air as well as logistical constraints for distribution of antibiotics and other potential interventions.

Fig. 4 BASIS dry filter collector deployed by LANL in Salt Lake City for the 2002 Olympics (Dennis Imbro and Wiley Davidson)

The BASIS system that was deployed to the Olympics was a distributed network of collectors with a central processing laboratory. The collectors utilized dry filters. Wet collectors were considered at the time but we were unable to achieve reliable performance in cold weather. A team of couriers would install clean filters and bring used filters to the central laboratory. The laboratory utilized a trained team that processed the filters in several steps—mostly by hand. Polymerase chain reaction (PCR) was used for the first pass biological assays. This was selected in 2000 based on PCR's limit of detection as well as a newly created capability to discover highly specific nucleic acid signatures compatible with PCR TaqMan™ detection. Commercially available instrumentation was used in the laboratory. Through an important collaboration with the Centers for Disease Control and Prevention, a process for taking signatures into assays and then public health validation was established. A chain-of-custody compliant tracking system that addressed good laboratory information management as well as law enforcement issues was incorporated into the laboratory protocols.

Because the event was highly visible and only a couple weeks duration, most of the emphasis was on performance that met the event organizers, public health, and law enforcement requirements. Cost is always an issue at some level, but little emphasis was placed on reducing operational costs for the deployment itself. For example, if more samples were required, additional shifts of personnel were scheduled in lieu of other options like laboratory automation.

The BASIS system performed to specifications for the intended application—special event biomonitoring.

Automated Detection Systems

For BASIS, personnel costs dominate with frequent sample collections. There are also all the challenges associated with increasing personnel levels for surge capacity. Several enhancements to the BASIS architecture that increase multiplexing in the central laboratory and add higher throughput and personnel reducing protocols have been made. For instance, microtiter format for

many of the laboratory steps has been demonstrated allowing both reductions in staff levels and higher throughput. The personnel costs for retrieving samples from the network of collectors need to be addressed as well.

One strategy that addresses the personnel costs is to incorporate the laboratory into the collector unit and create a network of detectors. One such system is the Autonomous Pathogen Detector System (APDS) [1, 2]. Each of these autonomous detector systems, see Fig. 4, collects air into a liquid and performs assays in the same chassis, and reports the results back to a central command center. The APDS performs both antibody and PCR assays, therefore increasing the statistical performance of the system. Even if samples are taken and processed every hour, the APDS can stay on-station without personnel attention for over a week.

Fig. 5 The LLNL Autonomous Pathogen Detector System (APDS) during field testing (John Dzenitis)

Because the system is automated, it can manipulate very small volumes. This reduces reagent consumption compared to manual systems as well as reducing potential sample handling errors.

There are other automated biodetection systems [3]. Perhaps most notably is the Department of Defense Joint Biological Point Detector System (JBPDS). There are also several systems in development that promise a new level of performance.

Rapid Detection and the Future

With the reduction of personnel costs and reagent consumption, autonomous systems are providing tremendous advantages. Current biodetection requirements for false positive rate motivated utilization of PCR and antibody detection. These approaches are currently slow. Although there are various methods for speeding up the current assays, as we look to the future it is worth considering approaches that are rapid and reagent-less. The three approaches discussed are optical detection, mass spectrometry detection, and all solid-state detection.

Optical Detection

Various types of optical systems have been evaluated for detecting biological aerosols. These systems are very fast response and only moderately priced. The limitation is a lack of specificity. Using optical techniques, it has proven difficult to reliably identify pathogens and discriminate them from various backgrounds and non-pathogenic but similar microbes. Optical detection currently addresses the application where rapid detection is needed to trigger a more specific

follow-up assessment. The optical trigger can also alert the operators that low regret responses could begin.

Mass Spectrometry

The Biological Aerosol Mass Spectrometer (BAMS) developed by LLNL [4], analyzes single aerosol particles in a few milliseconds. The system performs several measurements on the single particles including time of flight mass spectrometry. The system runs continuously, consumes no reagents, and is nearly instantaneous. BAMS is capable of discriminating among many types of particles and may eventually have species-level characterization although genus-level is more likely. Cost is currently the primary inhibitor to routine use.

As with optical systems, BAMS can be used as a trigger. It addressed an important application by debunking and triaging hoax mail packages after the October 2001 attacks. Because the system can identify many of the materials that were being used as hoax anthrax, BAMS could prioritize thousands of mail packages for additional testing.

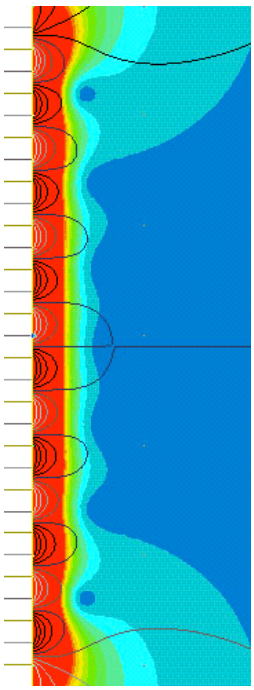

Fig. 6 Simulation of a solid state detector (Jay Javedani)

Solid State Detectors

This section focuses on nucleic acid detection only. In describing the ideal detector—rapid, specific, reagentless, and low false alarm, it is tempting to consider PCR the ideal. PCR exploits the hybridization of complementary strands of DNA and uses an enzyme to accelerate the process. Nature provided both of these advantages and one option is to design (or discover) better enzymes. It is also possible to consider replacing the hybridization. PCR, microarrays and other approaches exploit complementary base pairing and hybridization.

Here we consider the possibility of synthesizing a complementary strand of DNA using only solid state components. An example is shown in Fig. 6. For simplicity a uniform grid was used and the nucleic acid strand is replication of the same base. For this relatively small simulation, edge effects of the semiconductors are dominant.

Summary

Biodetection has come a long way. Operational systems are performing millions of assays with no false positives. However, there is much left to do. The detectors themselves can be improved in areas like cost and speed. The signatures being used today have also pushed the envelope of the supporting biology.

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Acknowledgements

The author acknowledges and thanks work sponsored by the Department of Homeland Security, Department of Defense including DARPA and DTRA, and the National Nuclear Security Administration. Critical collaborations in law enforcement and public health—especially the Centers for Disease Control and Prevention are gratefully acknowledged.

This work was performed under the auspices of the U.S. Department of Energy by University of California, Lawrence Livermore National Laboratory under Contract W-7405-Eng-48. UCRL-PRES-211707